

REMARKS

Applicants request entry of the amendment, reexamination, and timely notice of allowability.

The title has been amended to better reflect the pending claims.

Claims 66 and 85 have been amended to clarify the immunosuppressive agent groups listed. The Examiner suggested that these claims, and claims 67 and 86 dependent upon them, were indefinite in the recitation of these groups. As explained below, the group of immunosuppressive agents includes both monoclonal and polyclonal antibodies. No new matter enters through the amendment.

Claims 68 to 108 are pending and are being examined.

Rejection under 35 U.S.C. § 112, second paragraph.

Claims 66, 67, 85, and 86 stand rejected under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

The Examiner pointed to the language “and a monoclonal or polyclonal antibody” and asked whether the group contained a monoclonal antibody or a polyclonal antibody or both (*see* page 2 of Paper No. 26). Applicants respectfully suggest that this language clearly allows one to select either a polyclonal or monoclonal antibody. To expedite prosecution, applicants have amended the claims by replacing the phrase above with “or a monoclonal antibody or polyclonal antibody.” The amended language makes clear that either a monoclonal antibody or a polyclonal antibody can be selected.

The amended claims reflect the broadest definition of the group of immunosuppressive agents, where the immunosuppressive agent comprises either a monoclonal antibody or a polyclonal antibody, or any of the other agents listed. Accordingly, the amendment to the claims does not limit the subject matter claimed. Furthermore, the amendment is not made for reasons of patentability.

Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph.

Claims 82, 88, and 107 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully disagree.

Each of claims 82, 88, and 107 recite a gp19k sequence containing one or more point mutations wherein the gp19k protein retains an immunosuppressive activity. When presenting these claims in the prior response (Proposed Amendment After Final Rejection, dated February 15, 2002), applicants included an explanation of how the subject matter is supported by the specification. Applicants also specifically pointed to naturally occurring strains of adenovirus that include differing gp19k sequences. One of skill in the art would have known of these sequences and how they are relevant to this invention and the alteration of a gp19k sequence. Clearly, one of skill in the art would require little additional information to understand what gp19k sequences could be used in the invention.

Applicants also note that the specification at, for example, page 18, lines 15-20, emphatically states that genes with similar functional properties can be obtained by any technique known to a person skilled in the art and then used to construct the vectors of this invention. Applicants do not see why this emphatic statement is discounted in this case or why this statement does not apply to a gp19k protein as recited in the claims. One skilled in the art would not logically exclude gp19k sequences from the clear meaning this emphatic statement makes. On the contrary, since there are several immunosuppressive sequences disclosed in the specification, one of skill in the art would naturally read the statement at page 18, lines 15-20, and also the specification as a whole, to apply to the gp19k sequence. The arguments in Paper No. 26 do not suggest why the teachings of the specification or the emphatic statement at page 18 should be limited in its meaning here. Accordingly. Applicants respectfully submit that claims 82, 87, and 107 are supported by the specification as a whole.

To further support these applicants showing, applicants enclose two published papers available to one of skill in the art at the time this application was filed (Flomenberg *et al.*, J. of Virol. 62:4431-4437 (1988) and Hermiston *et al.* Virology 197:593-600 (1993)). Both of these papers show the sequence of a gp19k protein from adenovirus. By comparing even just the first few amino acids of these proteins, one of skill in the art would immediately recognize that point mutations can be made in the gp19k sequence without altering activity. For example, Flomenberg at page 4433 displays a gk19.2k sequence as beginning M G A I L V V, with the final V encoded by the codon GTG. Hermiston at page 597 displays a gp19k sequence as beginning M G A I L V L, with the final L encoded by the codon CTG. The two sequences differ by a point mutation that results in a single amino acid difference. Both of these proteins

operate in a viable viral strain, indicating that the point mutation or the differences between the sequences did not inhibit viral activities.

Thus, one of skill in the art clearly knew that mutations in the adenoviral gp19k sequence could be made and clearly knew that a variety of sequences already existed from which one could select mutation sites or compare sequences. With this knowledge and the ability to make sequence changes (the specification specifically notes site-directed mutagenesis at page 31, line 28, through page 32, line 4), one of skill in the art would have immediately recognized the point mutations possible in gp19k.

In addition, the instant specification specifically addresses how one of skill in the art uses the gp19k protein in the methods and compositions of the invention (*see, for example*, page 13, line 21, through page 14, line 5). An assay to test for the immunosuppressive activity of the adenoviral vector is presented in the experiments of Example 2, for example, beginning at page 38 of the specification. There is no further description required for one of ordinary skill in the art to recognize that changes in the gp19k protein are possible, especially since one of skill in the art already knew of various sequences that contained such changes.

Paper No. 26 suggests that disclosing techniques to identify gp19k proteins is irrelevant to introducing point mutations to the gp19k protein that retain immunosuppressive activity. This cannot be the case here because it is the understanding of one of skill in the art that must be considered (*see Vas-Cath Inc. v. Mahurkar*, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991)). One of skill in the art, as shown above, knew of gp19k sequence variations. One of skill in the art could also immediately recognize how this information is used in conjunction with the specification's assay on how to identify immunosuppressive adenoviral compositions according to the claimed invention and the specification's emphatic statement that other sequences with similar function

can be used (*see* page 18 of the specification). This is all one of skill in the art would need to recognize that the applicants invented the claimed invention.

Applicants respectfully request withdrawal of this rejection.

Claims 102-108 stand rejected under 35 U.S.C. § 112, first paragraph, as the specification allegedly fails to describe the subject matter in such a way as to enable one skilled in the art to make and/or use the invention. Applicants respectfully disagree.

The invention of claims 102-108 employ a recombinant adenoviral vector that can be used in a variety of expression systems and thus can be used for introducing a “sequence of interest” into a cell. The adenovirus has been shown to markedly prolong the expression of a sequence of interest (*see* Example 2.3 at page 42, for example). Accordingly, the use of the adenoviral vector in conjunction with an immunosuppressive agent is enabled by the description of the vector and the demonstration of its use, which applicants have already shown. The nature of the “sequence of interest” does not effect the novel expression-prolonging characteristics of the vector. Claims 102-108 encompass this expression-prolonging characteristic since the survival of the expressing cell is obviously connected to the ability to express a sequence of interest from the cell.

Accordingly, applicants have demonstrated the general principle of a gp19k-bearing adenovirus and an immunosuppressive agent to prolong cell survival. One of skill in the art would not consider the “sequence of interest” a particularly relevant concern for the production and use of this vector. Even if a particular “sequence of interest” could affect the ability to use the methods of the invention, one of skill in the art would be able to identify any effect through the assays and methods given in the specification without undue experimentation.

Paper No. 26 suggests that the specification only discloses a decrease in certain immune cells or the decrease in cytotoxic activity (*see* page 5). As noted above, Example 2.3, at least, specifically shows the prolonged expression of a sequence of interest, here represented by b-gal. If there is some objective reason why one of skill in the art would doubt that another sequence of interest results in an ineffective vector, it has not been clearly presented to applicants.

Further, there is no requirement that the "sequence of interest" provide some activity to prolong expression. The exemplary use of b-gal as the sequence of interest would seem to make this point very clear. Accordingly, applicants need not show how p53, aFGF, bFGF, factor VII, or any other sequence of interest results in prolonged expression (*see* page 5 of Paper No. 26). There is no objective reason for one of skill in the art to conclude that the sequence of interest, or any of the genes listed, could destroy or affect the expression-prolonging characteristics of the claimed invention. Thus, a *prima facie* case of lack of enablement has not been made.

Applicants respectfully request withdrawal of this rejection.

Rejection under 35 U.S.C. § 103(a).

Claims 65-81, 83-87, and 89-101 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Leibowitz et al. in view of Linsley et al. and Nabel et al. Applicants respectfully disagree.

Applicants respectfully point out that a prior § 103 rejection based upon the primary reference Leibowitz et al. and a different combination of secondary references, which combination included the same Linsley et al. document cited here, was overcome by applicants' arguments in the Amendment and Reply filed December 8, 1999 (*see* Office Action of February 25, 2000). The persuasive arguments from that Amendment and Reply apply equally well to this

rejection as the newly cited Nabel et al. document does not to remedy the deficiencies of the combination of references. For example, Nabel et al. nowhere teaches or suggests a composition comprising an immunosuppressive agent and an adenoviral vector as claimed here.

Applicants respectfully submit that this rejection improperly uses a hindsight analysis to reconstruct the claimed invention and/or provide the required motivation to combine the alleged teachings to arrive at the claimed invention. In fact, none of the documents cited even suggests combining an immunosuppressive agent with an adenovirus. There is simply no objective reason to combine the cited documents as has been done in Paper No. 26 to justify this rejection.

The Linsley document discusses the CTLA4Ig molecule. It suggests that this molecule can be used in transplantation or antibody-mediated autoimmune disease (*see* third column of page 794). The document nowhere mentions an adenovirus. Furthermore, it nowhere suggests how or why one would consider CTLA4Ig for other treatments or methods, and it especially does not suggest a method employing an adenoviral vector. At best, Linsley discusses the existence of one of the immunosuppressive agents recited in applicants' claims.

Neither Nabel nor Leibowitz provide any objective motivation to combine an adenoviral vector with an immunosuppressive agent. The Examiner acknowledges that Leibowitz "does not teach combination of an immunosuppressive agent, such as CTLA4Ig, and a recombinant adenovirus" (*see* page 8 of Paper No. 26). The Examiner does not discuss Nabel in this respect. However, importantly, page 250 of Nabel indicates that while the issue of "gene persistence" exists for adenoviral vectors, no solution is suggested. Applicants' claimed invention demonstrating prolonged expression specifically addresses this issue. However, no statement, teaching, or suggestion from any of the cited documents does. Using applicants' success as a motivation to combine the documents here is improper hindsight. Twisting the identification of

a “gene persistence” issue into a motivation to arrive at applicants’ claimed invention is also improper, as the issue could at best be a motivation to look for any solution, but certainly not the solution applicants’ disclose in their specification.

Paper No. 26 alleges that it would be obvious to combine the teachings because “immunosuppressive agents such as CTLA4Ig can suppress T-cell dependent antibody response and E19pk protein can alter the presentation of MHC class I cell surface antigen to reduce transplant rejection by the recipient organism’s immune system and combining said agent and adenovirus would enhance their immunosuppressive effects” (*see* pages 8-9 of Paper No. 26). Applicants are confused by this statement. It seems to discuss immunosuppressive agents, but nowhere addresses why one would combine them with an adenoviral vector or an adenoviral vector comprising a gp19k sequence.

Applicants’ cannot see any relevance for the MHC class I issue. Even if Leibowitz discusses MHC class I in conjunction with transplants, what relevance does this have to adenoviral vectors. And as shown above, while Nabel may discuss an adenoviral vector, Nabel does not even offer a suggestion for resolving or even addressing the “gene persistence” issue. In fact, no statement from any of the cited documents supports the type of motivation applied in Paper No. 26.

Applicants respectfully submit that a fair reading of the contents of the cited documents provides no motivation to combine. As discussed below, it is only improper conclusory statements based upon the much more general immunosuppression information noted from the documents that supports an alleged motivation.

As noted in the *In re Lee* decision (61 U.S.P.Q.2d 1430 (Fed. Cir. 2002), “[the] case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based

obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references" (*citing* In re Dembiczak, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999)). Applicants submit that the rejection merely identifies particular immunosuppressive aspects noted in the documents cited. While each of the documents may discuss immunosuppression in some way, or an immune response, no objective teaching suggests combining an immunosuppressive agent with an adenoviral vector or an adenoviral vector comprising a gp19k sequence. It is only with improper hindsight or improper conclusory statements that one could arrive at applicants' claimed invention from these cited documents.

Applicants respectfully submit that the rejection fails to satisfy the requirement for a motivation to arrive at applicants' claimed invention. A motivation based simply on immunosuppression or immune response information cannot lead one to applicants' claimed invention. Information on immunosuppression can be at best a general motivating factor. A specific motivation to arrive at the claimed combination is required.

Applicants also submit that the evidence in applicants' specification demonstrates unexpected results in prolonging expression. As stated previously (*see* Amendment filed December 8, 1999) and as shown in the specification (*see* Example 2.3), the markedly greater expression period resulting from applicants' claimed invention could not have been expected from a simple juxtaposition of the respective effects of an immunosuppressive agent and a recombinant adenovirus comprising a gp19k sequence.

For these reasons, applicants submit that a *prima facie* case of obviousness has not been made and that even if it has, applicants' expected results demonstrate that the claimed invention is patentable.

Conclusion

Applicants believe that this application is now in condition for allowance. If the Examiner believes that prosecution might be furthered by discussing the application with applicants' representative, in person or by telephone, we would welcome the opportunity to do so.

If additional extension of time fees, requests for extension of time, or petitions are necessary to enter and/or consider this paper, applicants hereby petition or request an extension of time. For any fees required, including additional claim fees, in order to enter or consider this paper or keep this application pending, applicants' representative hereby authorizes the Commissioner to charge Deposit Account No. 50-1129. If there is any variance between the fees submitted and any fee required, including the extension of time fee and the fee for net addition of claims, the Commissioner is hereby authorized to charge or credit Deposit Account No. 50-1129.

Respectfully submitted,
Wiley Rein & Fielding LLP

Date: February 6, 2003

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Enclosures: Flomenberg et al.
Hermiston et al.
Appendix Showing Marked-up Version of Claims

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Appendix Showing Marked-up Version of Claims

66. (Amended) The composition according to claim 65, wherein the immunosuppressive agent is selected from cyclosporin, FK506, azathioprine, a corticosteroid, [and] or a monoclonal antibody or [a] polyclonal antibody that is able to inactivate an immune molecule or induce destruction of an immune cell carrying these molecules.

85. (Amended) The method according to claim 83, wherein the immunosuppressive agent is selected from cyclosporin, FK506, azathioprine, a corticosteroid, [and] or a monoclonal antibody or [a] polyclonal antibody that is able to inactivate an immune molecule or induce destruction of an immune cell carrying these molecules.